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MSK.P-003-US
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Sirotnak et al.
Serial No.: 09/214,984 Examiner : R. Sripada
Filed : March 8, 1999 Group Art Unit : 1611
For : Purified Compositions of 10-Propargyl-10-Deazaminopterin and Methods of Using Same in the Treatment of Tumors

AMENDMENT

October 20, 1999

Asst. Commissioner for Patents
Box No Fee - Amendment
Washington, D.C. 20231

Sir:

This is in response to the Official Action mailed July 20, 1999 for the above-captioned application. Reconsideration of the application in view of the remarks herein is respectfully requested.

Claims 2 and 9 stand rejected under 35 USC 112, second paragraph. In making this rejection, the Examiner has not addressed the standards routinely applied in considering the definiteness of the claims, i.e., the ability of a person skilled in the art to understand what falls within the scope of the claims, and has therefore failed to meet the burden imposed by cases such as *Ex parte Cordova*, 10 USPQ 2d 1949, 1952 (POBAI 1987) to specifically identify why this standard is not met. Thus, the rejection under section 112 is plainly deficient.

Turning to the specific statements made in the support of the rejection, the Examiner rejected claim 2 under 35 USC 112, second paragraph, stating that it was indefinite as a

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20 October, 1999
Date of Signature

result of the use of the term "composition." Applicants respectfully point out, however, that compositions of matter are a statutory class of patentable subject matter as defined in 35 USC 101. Thus, the term is included in the claim to identify that the claim is directed to a composition, as opposed to a method or apparatus. This does not render the claim indefinite. Indeed, the Examiner's objection appears to be not that a person skilled in the art would be unable to identify whether or not a material was a composition, or that they would be unable to ascertain whether a given composition contained the recited ingredients. Rather, the Examiner objects because the claim encompasses materials not specifically recited. It is pointed out, however, that the term "comprising" is routinely used in claims to define this very circumstance. For example, MPEP § 2111.03 states:

> The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open - ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc.* , 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986) *In re Baxter*, 656 F.2d 679, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948)("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

Thus, Applicants submit that the use of the term composition can hardly be considered to render a claim *per se* indefinite for the reasons given by the Examiner.

With respect to claim 9, the Examiner states that the claim is indefinite because of the phrase "at least one additional cytotoxic or antitumor compound." According to the Examiner, the claim must identify the specific compound if it is to comply with section 112. Applicants point out, however, that generic phrases are frequently used in claims without running afoul of section 112. Indeed, in *In re Skoll,* 187 U.S.P.Q. 481 (C.C.P.A. 1975), the CCPA found that the term "organic or inorganic acid" was broad, but not indefinite. Absent a clearly stated reason why the Examiner believes that a person skilled in the art could not understand whether a given composition met the limitations of claim 9, the rejection under 35 USC 112 second paragraph should be withdrawn.

On the merits, the Examiner rejected claims 1-12 under 35 USC 103 as obvious over US Patent No. 5,354,751 ("the '751 patent"). The difference between the claimed invention is the level of purity of the compositions of the invention, and in particular the removal of 10-deazaminopterin from the 10-propargyl-10-deazaaminopterin (PDX). The Examiner asserts that such compositions would have been obvious, because persons skilled in the art would recognize the desirability of having a pure therapeutic agent to remove impurities that are potentially toxic. Applicants submit that this argument is in error for several reasons.

First, it must be appreciated that when dealing with chemotherapy agents, the drug is inherently toxic, and high levels of cytotoxicity are desirable. Thus, the Examiner's statement that purification to remove toxic impurities would be a goal of the artisan represents something of a *non sequitur*.

Second, there is nothing in the cited reference which would lead the person skilled in the art to believe that the preparation of PDX disclosed in the '751 patent contains impurities which should be removed. Since the compositions in the '751 patent were utilized in animal models, it is reasonable to presume that the level of purity was satisfactory.

Third, the impurity which was found to be detrimental to the activity of the compositions of the invention is itself an active antifolate. Nothing in the art suggests that the incorporation of this compound would detract from the activity of the PDX. Nevertheless, it is apparent from the dosages utilized and the results obtained in the present application compared to the prior art, that the impurity is not one which merely increases toxicity of the composition, but rather is one which negatively effects the activity of the active PDX. Thus, in the '751 patent, the lowest dose tested in mice was 24 mg/kg of a composition that was 95% pure. Thus, a total of 22.8 mg/kg of PDX was administered in the study of the '751 patent. In contrast, in the experiments reported in the present application, better results were obtained using dosages of 3 mg/kg of a 98% pure compound, i.e,. upon administration of only 2.94 mg/kg. This negative synergy of the impurity on the activity of PDX was not known and could not have been predicted.

In considering the issue of obviousness of a chemical composition under 35 USC § 103, the Examiner must consider not only the physical nature of the composition, but also the properties of the composition. Otherwise, the Examiner has failed to follow the statutory mandate to consider the invention **as a whole**. *Jones v. Hardy*, 220 USPQ 1021, 1025 (Fed. Cir. 1984) ("Failure to consider the claimed invention as a whole is an error of law"); In re Kuehl, 177 USPQ 250, 255 (CCPA 1973) ("The test under §103 is whether in view of the prior art the invention as a whole would have been obvious at the time it was made"). In this case, the purified compositions (including their inherent properties which provide for increased activity) would not have been obvious.

For the foregoing reasons, Applicants submit that the application is in form for allowance. Favorable reconsideration and allowance of all claims are respectfully urged.

Respectfully submitted,

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